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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/628,495 | 07/28/2000 | David White | 210147.0039/16U1 | 3801 |

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| EXAMINER |
|---|
| NICHOLS, CHRISTOPHER J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 18 |

DATE MAILED: 09/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/628,495 | WHITE, DAVID | |
| | Examiner | Art Unit | |
| | Christopher Nichols, Ph.D. | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25-31,37,38 and 42-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-31,37,38 and 42-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,11,16* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group X (Claims 25-31, 37, and 38) with the addition of claims 42-72, in part drawn to methods of determining whether a test compound alleviates a bone-related disorder requiring determining MRR protein activity in Paper No. 17 (9 August 2002) is acknowledged. Claims 1-24, 32-36, and 39-41 are cancelled.

### *Status of Application, Amendments, and/or Claims*

2. The claims amendment of 9 August 2001 (Paper No. 17) has been entered in full. Claims 1-24, 32-36, and 39-41 are canceled. Claims 42-72 have been added. Claims 25-31, 37-38, and 42-72 are under examination.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

### *Specification*

4. The Specification is objected to because of the following informalities: "G proteins" is missing a hyphen (pp. 2 lines 3-5), "Bio/technology" is misspelled (pp. 54 line 8), Sentence ends with ">" not a period (pp. 11 line 22) and ";" not a period (pp. 16 line 32), "Carboxyl terminal" missing hyphens (pp. 26 lines 24; pp. 27 line 1; pp. 34 line 27), "Amino terminal" missing hyphen (pp. 26 lines 31; pp. 27 lines 11 and 14; pp. 35 line 17; pp. 35 line 6), the following

should be italicized: E. coli, in vitro, in situ, in vivo (throughout Specification), and provide definition for "GST-" (pp. 28 line 22). Appropriate correction is required.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pp. 48 line 4). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 25-31, 37-38, and 42-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 25 is directed a method of determining whether a test composition is useful for alleviating a bone-related disorder. Claims 26 and 57-64 are directed to bone-related disorders pertaining to the method of Claim 25. Claim 27 is directed to the SEQ ID which comprising the MRR protein. Claims 28 and 42-44 are directed to types of MRR activity that are measured in the method described in Claim 25. Claims 29-31 and 45-46 are directed to the type of cells that are to be used in the method according to Claim 25. Claims 37 is directed a method of determining whether a test composition is useful for determining the propensity of a

test compound to induce a bone-related disorder in a human patient. Claims 38 and 65-72 are directed to bone-related disorders pertaining to the method of Claim 37. Claim 47 is directed to the SEQ ID which comprising the MRR protein. Claims 48-51 are directed to types of MRR activity that are measured in the method described in Claim 37. Claims 52-56 are directed to the type of cells that are to be used in the method according to Claim 37.

7. The specification teaches that bone-cells are designated osteoblasts, which deposit bone tissue and osteoclasts, which reabsorb bone tissue. Bone-related disorders cover two general classes, those that result in an increase in bone density and those, which result in a decrease in bone density. The phrase bone-related disorders encompass several disorders involving different mechanisms such as aberrant deposition, reabsorption, or configuration of bone tissue. Proteolytic activity (e.g. ability of the carboxyl terminal portion of MRR protein to cleave a peptide bond of a polypeptide, ability to cleave an aminoacyl bond of a polypeptide), a pore-modulating activity (e.g. ability of MRR protein to activate or de-activate a transmembrane protein pore, ability to "open" a transmembrane pore, that is, to render the transmembrane protein capable of facilitating passage or a compound from one side of the cytoplasmic membrane to the other), an enzyme-modulating activity (e.g. ability of MRR protein to modify an enzyme in a manner that increases or decreases the enzyme's activity, ability to activate of a nucleotide cyclase enzyme), and a gene transcription-modulating activity (e.g. ability of MRR protein to enhance or inhibit expression of gene, ability to enhance transcription of a gene). While general guidance is provided regarding preparing an in vitro system to execute the invention, no working examples are provided re: screening compounds that effect MRR in relation to alleviation of bone-related disorders.

8. The art teaches that bone-related disorders can cover any and all maladies related to the skeletal system including but not limited to fractures, compression, tumors, osteoporosis, osteomalaica, genetic defects, nutritional defects, injuries, and the like (Stedman's Medical Dictionary). Proteolytic activity covers several classes of enzymes that hydrolyze peptide bonds including but not limited to chymotrpsin, trypsin, (Murray et al., Harper's Biochemistry). Pore-modulating activity includes channels, pumps, and some carriers. Each of which is an enormous class of peptide and non-proteinaceous structures (Stein, Channels, Carriers, and Pumps). Enzyme-modulating activity can cover inhibitors, enhancers, coenzymes, and all the subtypes therein (Murray et al., Harper's Biochemistry). Gene transcription-modulating activity encompasses enhancers, inhibitors, regulators, operons, suites, transcription factors, suppressors, TATA boxes, Kozak sequences, and little understood untranslated regions (Lewin, Genes II; Murray et al., Harper's Biochemistry). In addition, any of the above mentioned modulators of proteolytic activity, pores, enzymes, and/or genes can be proteinaceous, organics, and/or pharmaceuticals (Murray et al., Harper's Biochemistry). Bone cells are primarily osteoclasts and osteoblasts, although it can encompass hematopoietic cells as they are generated in the bone marrow (Stedman's Medical Dictionary).

9. Thus the claimed invention is directed to an *in vitro* system for screening compounds that act on or via MRR, which may alleviate bone-related disorders, which is not supported by the teachings of the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specific biological actions/activities that the compounds would effect; How does the effect on MRR relate to symptoms of a wide range of bone-related disorders; Expectation of MRR to be involved in one or any bone-related

disorder. The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

10. Regarding bone-related disorder, the art recognizes that bone-related disorder includes a wide variety of diseases, disorder, syndromes, and injuries. Due to the large quantity of experimentation necessary to evaluate all the possible bone-related disorder, the lack of direction/guidance presented in the specification which bone-related disorder, the absence of working examples directed to bone-related disorders, the complex nature of the invention, the unpredictability of the effects of the effects of test composition on a bone-related disorder (Stedman's Medical Dictionary), and the breadth of the claims which fail to recite limitations for which bone-related disorder, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

11. Regarding proteolytic activity, the art recognizes that proteolytic activity includes a great variety of enzymatic site specificity, conditions, and resultant proteolytic products. Due to the large quantity of experimentation necessary to evaluate all the possible proteolytic activities, the lack of direction/guidance presented in the specification which proteolysis the test composition would be, the absence of working examples directed to proteolytic activities, the complex nature of the invention, the unpredictability of the effects of a protease on peptides (Murray et al., Harper's Biochemistry), and the breadth of the claims which fail to recite limitations for what effects proteolytic activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

12. Regarding pore-modulating activity, the art recognizes that pore-modulating activity includes a great variety of enzymatic activities, whether enhancing, inhibiting, blocking and to what degree of modulation, and conditions. In addition, pores are also known as channels in the art. Due to the large quantity of experimentation necessary to evaluate all the possible pore-modulating activities, the lack of direction/guidance presented in the specification which pore-modulating effects of the test composition would be, the absence of working examples directed to pore-modulating effectors, the complex nature of the invention, the unpredictability of the effects of pore-modulators on cells (Stein, Channels, Carriers, and Pumps), and the breadth of the claims which fail to recite limitations for what effects pore-modulating activity would have on cells, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

13. Regarding enzyme-modulating activity, the art recognizes that "enzyme" includes a great variety of enzymes. Due to the large quantity of experimentation necessary to evaluate all the possible enzymes, the lack of direction/guidance presented in the specification which enzymes, the absence of working examples directed to enzyme-modulation effectors, the complex nature of the invention, the unpredictability of the effects of enzyme-modulators on cells (Alberts et al., Molecular Biology of the Cell; Murray et al., Harper's Biochemistry), and the breadth of the claims which fail to recite limitations for what effects enzyme-modulating activity would have on cells, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. Regarding gene transcription-modulating activity, the art recognizes that "transcription-modulating" includes a great variety of effects whether inhibiting, enhancing, or terminating.

Due to the large quantity of experimentation necessary to evaluate all the possible effects on transcription, the lack of direction/guidance presented in the specification on what type of transcription modulation, the absence of working examples directed to transcription-modulation, the complex nature of the invention, the unpredictability of the effects of transcription-modulators on cells (Lewin, Genes II; Murray et al., Harper's Biochemistry), and the breadth of the claims which fail to recite limitations for what effects transcription-modulating activity would have on cells, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Regarding bone cell, the art recognizes that bone cell includes a group of cell types including but not limited to osteoclasts, osteoblasts, and some stem cells. Due to the large quantity of experimentation necessary to evaluate the use of all possible bone cell types, the lack of direction/guidance presented in the specification which kind of bone cells should be used, the absence of working examples directed to bone cells, the complex nature of the invention, the unpredictability of culturing bone cells (Stedman's Medical Dictionary), and the breadth of the claims which fail to recite limitations for which bone cells and under what conditions to be maintained, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

16. Finally, the application must establish a nexus between the protein recited in the claims and the disease state recited in the claims. In this case, the skilled artisan is not guided as to how a compound must affect one or more activates of the protein such that the compound would be determined to be one that alleviates or induces bone disease. Also, bone diseases are varied (see discussion and references above) and it is not clear that this protein is involved in a rate-limiting

step for any bone disease or disorder such that it could be used in a screening assay to identify therapeutic compounds.

17. Claims 25-31, 37-38, and 42-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The method steps do not indicate how the compound must affect the protein in order for the compound to be labeled "alleviator" or "inducer" as recited in preambles. Thus the claims are incomplete.

***Summary***

18. Claims 25-31, 37-38, and 42-72 are hereby rejected.

***Conclusion***

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kennedy

CJN
September 11, 2002